National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Adult Cancer Pain

V.1.2006

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Manuscript

References

This manuscript is being updated to correspond with the newly updated algorithm.

Clinical Trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Consensus

Summary of Guidelines Updates

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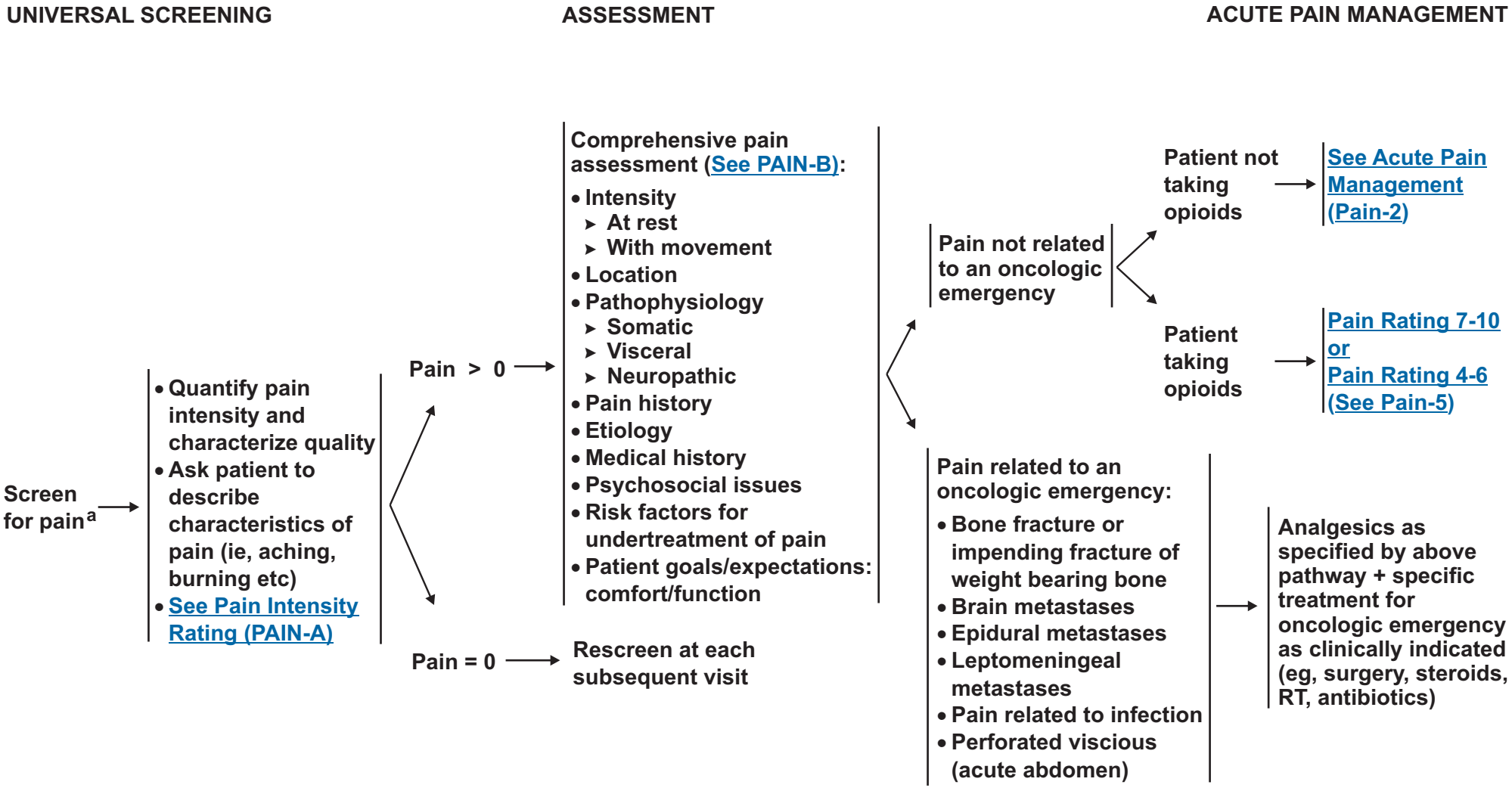

[a]Events that are expected to cause discomfort to the patient such as diagnostic and therapeutic procedures (IV, arterial line, central line, injections, manipulations, etc) as well as transportation/change in position for a patient with a fracture; should merit pre-treatment with an analgesic. Additional analgesics should be available immediately for further titration by the caregiver as needed.

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To quantify pain intensity, See Pain Intensity Rating (PAIN-A)

ACUTE PAIN MANAGEMENT

Opioid naive

Pain 7-10 (pain emergency) →
- Rapidly titrate short-acting opioid[b]
  - Begin bowel regimen[c]
- Recognize and treat side effects[c]
- Nonopioid analgesics as indicated[d]
- Provide psychosocial support[e]
- Provide patient and family education[f]

→ See Response to Severe or Moderate Pain with Short-Acting Opioids (PAIN-5) → Repeat comprehensive reassessment in 24 h

Pain 4-6 →
- Titrate short-acting opioid[b]
  - Begin bowel regimen[c]
- Recognize and treat side effects[c]
- Nonopioid analgesics as indicated[d]
- Provide psychosocial support[e]
- Provide patient and family education[f]

→ See Response to Severe or Moderate Pain with Short-Acting Opioids (PAIN-5) → Repeat comprehensive reassessment in 24-48 h

Pain 1-3 →
- Consider NSAID or acetaminophen without opioid if patient is not on analgesics[g]
  or
- Consider titrating short-acting opioid[b]
  - Begin bowel regimen[c]
- Recognize and treat side effects[c]
- Nonopioid analgesics as indicated[d]
- Provide psychosocial support[e]
- Provide patient and family education[f]

→ Repeat comprehensive reassessment in 24-72 h

→ See Subsequent Treatment for Acute Pain Management (PAIN-3)

[b] See Opioid Prescribing, Titration, and Maintenance (PAIN-C).
[c] See Management of Opioid Side Effects (PAIN-D).
[d] See Specific Pain Problems (PAIN-E).
[e] See Psychosocial Support (PAIN-F).
[f] See Patient and Family Education (PAIN-G).
[g] See NSAID and Acetaminophen Prescribing (PAIN-H).

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SUBSEQUENT TREATMENT FOR ACUTE PAIN MANAGEMENT

- Consider conversion to sustained-release agent with rescue medications as appropriate[b]
- Reassess and modify regimen to minimize side effects[c]
- Nonopioid analgesics as indicated[d]
- Provide psychosocial support[e]
- Provide patient and family education[f]

Pain 7-10 →
- Reevaluate opioid titration[b]
- Reevaluate working diagnosis
- Consider specific pain problems[d]
- Consider specialty consultations[h]

Pain 4-6 →
- Continue opioid titration[b]
- Consider specific pain problems[d]
- Consider specialty consultations[h]

Pain 1-3 → Reassess pain at least every week until comfortable, and then every visit → See Subsequent Follow-Up (PAIN-4)

See Response to Severe or Moderate Pain with Short-Acting Opioids (PAIN-5)

See Universal Screening and Assessment (PAIN-1)

See Interventional Strategies (PAIN-6)

Repeat comprehensive reassessment in 24 h

Repeat comprehensive reassessment in 24-48 h

Patient goals/expectations NOT achieved:
- Comfort
- Function

Patient goals/expectations ACHIEVED:
- Comfort
- Function

[b] See Opioid Prescribing, Titration, and Maintenance (PAIN-C).
[c] See Management of Opioid Side Effects (PAIN-D).
[d] See Specific Pain Problems (PAIN-E).
[e] See Psychosocial Support (PAIN-F).
[f] See Patient and Family Education (PAIN-G).
[h] See Specialty Consultations (PAIN-I).

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SUBSEQUENT FOLLOW-UP

Clinician issues/responsibilities

- Written follow-up plan
- Instruct the patient on the importance of the following:
  - Adherence to medication plan
  - Maintain clinic appointments
  - Follow-up with clinicians as indicated
  - Follow documented plan[f]
- Process realistic goals, revise and review
- Address system barriers
  - Social services
- On-call/prn availability
- Routine follow-up
  - Frequency at least every 3 months depending on:
    - Patient condition
    - Institutional/state standards

Goals of treatment ACHIEVED:

- Comfort
- Function

Goals of treatment NOT achieved:

- Comfort
- Function

→ See Universal Assessment and Screening (PAIN-1)
Consider Interventional Strategies (PAIN-6)

[f]See Patient and Family Education (PAIN-G).

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To quantify pain intensity, See Pain Intensity Rating (PAIN-A)

RESPONSE TO SEVERE, MODERATE, OR INCREASED PAIN WITH SHORT-ACTING OPIOIDS

(Monitor respiratory rate and sedation, consider monitoring oxygen saturation and vital signs)

Pain 7-10 or Pain 4-6 or As clinically indicated for pain crisis

- Oral (peak effect 60 min)
  - Not taking opioids → Dose 5-15 mg oral immediate-release morphine sulfate or equivalent
  - Taking opioids → • Calculate previous 24 h total requirement. • To calculate breakthrough dose take 10-20% of the previous 24 h total requirement and increase this by 50-100% and administer
- Intravenous[i] bolus (peak effect 15 min) administered by healthcare provider or patient-controlled analgesia
  - Not taking opioids → Dose 1-5 mg intravenous[i] morphine sulfate or equivalent
  - Taking opioids → Calculate previous 24 h total requirement, convert to total IV equivalent and increase by 10%

Initial Dose

Subsequent Dose

Reassess at 60 min / at 15 min

- Pain score unchanged or increased → Administer double dose
- Pain score decreased < 50% → Repeat same dose
- Pain score decreased ≥ 50% → • Continue at current effective dose prn • Reassess in 2-3 h to determine effective dose → • 24 h follow-up • Calculate total 24 h dose ▸ Convert to long acting ▸ Calculate breakthrough 10-20% of 24 h

→ Return to Acute Pain Management (PAIN-2) or Subsequent Treatment (PAIN-3)

[i]Subcutaneous can be substituted for intravenous, however subcutaneous route delays onset of effect by up to 30 minutes.

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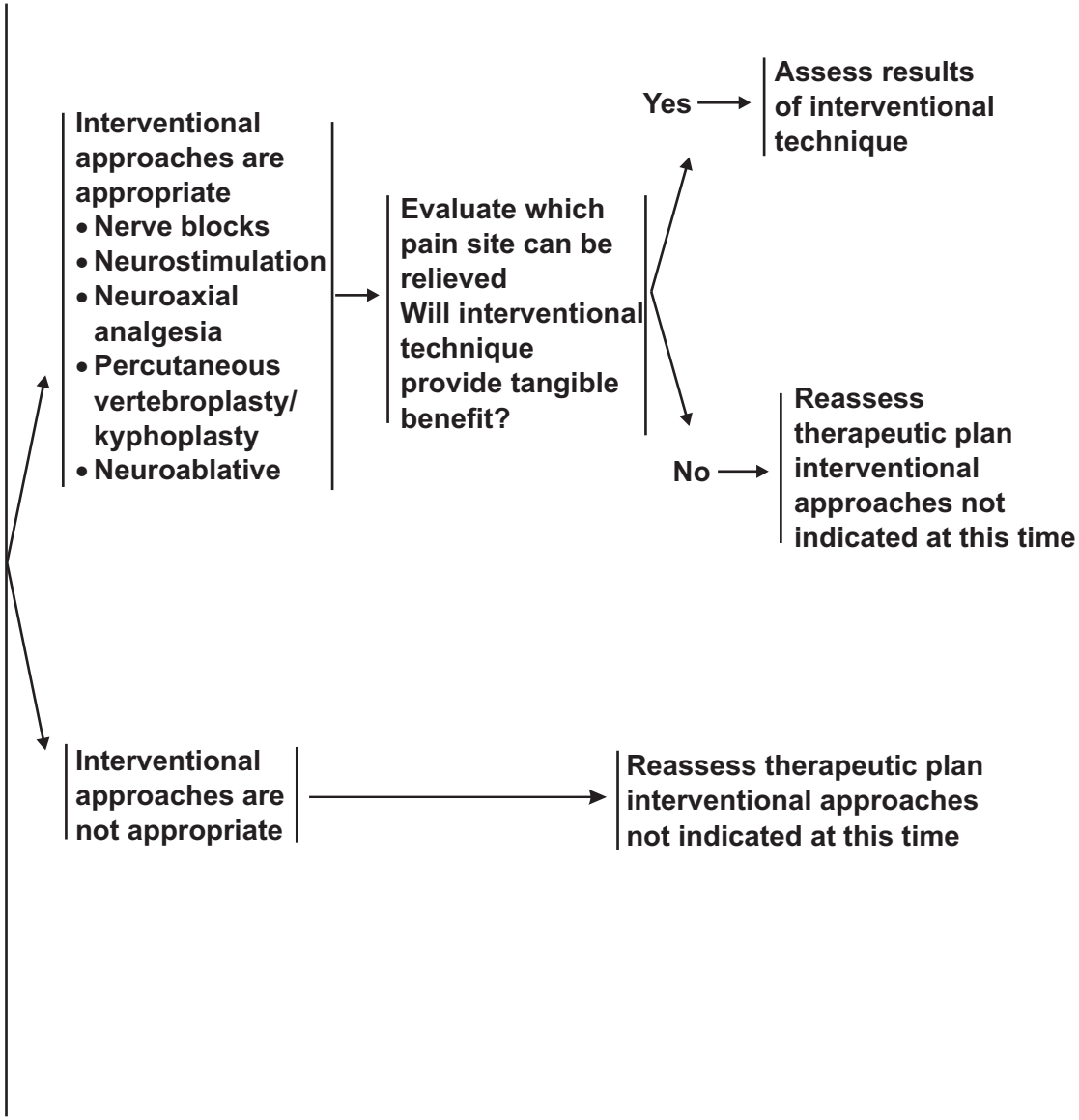
INTERVENTIONAL STRATEGIES

Interventional consultation[j]

- Major indications for referral:
  - Pain likely to be relieved with nerve block (e.g., pancreas/upper abdomen with celiac plexus block, lower abdomen with superior hypogastric plexus block, intercostal nerve, or peripheral nerve)
  - Failure to achieve adequate analgesia without intolerable side effects (may be handled with intraspinal agents, blocks, spinal cord stimulation, or destructive neurosurgical procedures)
- Commonly used procedures:
  - Regional infusions (requires infusion pump)
    - Epidural: easy to place, requires large volumes and an externalized catheter; for infusions of opioids, local anesthetics, clonidine, useful for acute post-operative pain
    - Intrathecal: easy to internalize to implanted pump; for infusions of opioids, local anesthetics, clonidine, and ziconotide
    - Regional plexus: for infusions of local anesthetics, to anesthetize single extremity
  - Neurodestructive procedures for well-localized pain syndromes
    - Head and neck: peripheral nerve block
    - Upper extremity: brachial plexus neurolysis
    - Thoracic wall: epidural neurolysis, intercostal neurolysis
    - Upper abdominal pain (visceral): celiac plexus block, thoracic splanchnicectomy
    - Midline pelvic pain: superior hypogastric plexus block
    - Rectal pain: intrathecal neurolysis, midline myelotomy or superior hypogastric plexus block
    - Unilateral pain syndromes: cordotomy
    - Consider intrathecal L/S phenol block
  - Percutaneous vertebroplasty/kyphoplasty
  - Neurostimulation procedures for cancer-related symptoms (ie, peripheral neuropathy)



[j]High benefits/risk ratio examples: celiac plexus, superior hypogastric plexus, and peripheral nerves.

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PAIN INTENSITY RATING (1 of 2)

Table 1: Numerical Rating Scale

Numerical rating scale:

- **Verbal: "How much pain are you having?" from 0 (no pain) to 10 (worst imaginable pain)**
- **Written: "Circle the number that describes how much pain you are having."**

0 1 2 3 4 5 6 7 8 9 10
No pain Worst imaginable pain

Categorical scale:

"How much pain are you having?"

None (0), Mild (1–3), Moderate (4–6), or Severe (7–10)

From Wong DL, Hockenberry-Eaton M, Wilson D, Winkelstein ML, Schwartz P: Wong's Essentials of Pediatric Nursing, 6/e, St. Louis, 2001, P. 1301. Copyrighted by Mosby, Inc. Reprinted by permission.

Pain Intensity Rating continued on next page

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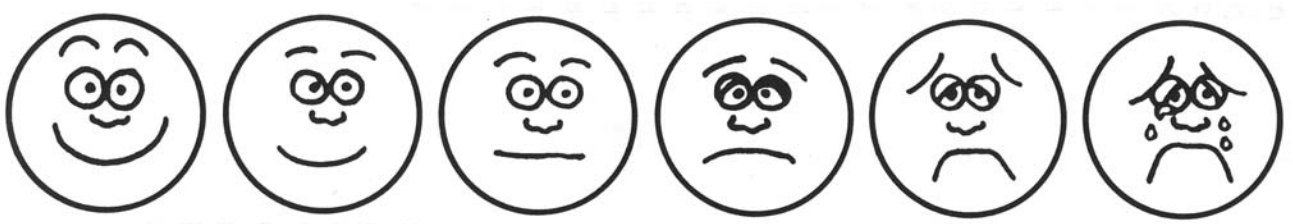
PAIN INTENSITY RATING (2 of 2)

Table 2: Wong-Baker FACES Pain Rating Scale



0	2	4	6	8	10
NO HURT	HURTS A LITTLE BIT	HURTS A LITTLE MORE	HURTS EVEN MORE	HURTS A WHOLE LOT	HURTS WORST

Explain to the person that each face is for a person who feels happy because he has no pain (hurt) or sad because he has some or a lot of pain. FACE 0 is very happy because he doesn't hurt at all. FACE 2 hurts just a little bit. FACE 4 hurts a little more. FACE 6 hurts even more. FACE 8 hurts a whole lot. FACE 10 hurts as much as you can imagine, although you don't have to be crying to feel this bad. Ask the person to choose the face that best describes how he is feeling.

Rating scale is recommended for persons age 3 years and older. See NCCN Pediatric Pain Guidelines
May be useful in adults with language barrier.
Brief word instructions: Point to each face using the words to describe the pain intensity. Ask the child to choose face that best describes own pain and record the appropriate number.

From Wong DL, Hockenberry-Eaton M, Wilson D, Winkelstein ML, Schwartz P: Wong's Essentials of Pediatric Nursing, 6/e, St. Louis, 2001, P. 1301. Copyrighted by Mosby, Inc. Reprinted by permission.

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Adult Cancer Pain

COMPREHENSIVE PAIN ASSESSMENT

History

- Pain
  - Intensity See Pain Intensity Rating (PAIN-A)
    - At rest
    - With movement
    - Interference with activities
  - Location
  - Pathophysiology
    - Somatic: pain in skin, muscle, bone described as aching, stabbing, throbbing, pressure
    - Visceral: pain in organs or viscera described as gnawing, cramping, aching, sharp
    - Neuropathic: pain caused by nerve damage described as sharp, tingling, burning, shooting
  - If patient is unable to communicate, consider alternative method to obtain pain rating and response.
  - History: onset, duration, course, aggravating, associated symptoms, alleviating factors, response to current and prior treatment including reasons for discontinuing
  - Etiology
    - Cancer
    - Cancer therapy or procedures
    - Coincidental or noncancer
  - Response to current therapy
    - Pain relief and side effects
    - Patient adherence to medication plan
- Medical
  - Current medications including prescribed, over the counter, complementary and alternative therapies
  - Oncologic
  - Other significant medical illnesses
- Psychosocial
  - Patient distress See NCCN Distress Guidelines
  - Family and other support
  - Psychiatric history including current or prior history of substance abuse
  - Special issues relating to pain
    - Meaning of pain for patient/family
    - Patient/family knowledge and beliefs surrounding pain
    - Cultural beliefs toward pain
    - Spiritual or religious considerations
- Risk factors for undertreatment of pain
  - Pediatric, geriatric, communication barriers, history of substance abuse, neuropathic pain, minorities, female, cultural factors
- Risk factors for aberrant use or diversion of pain medication
  - Patient factors
  - Environmental and social factors

Physical examination

Relevant laboratory and imaging studies

Return to Initial Screening (PAIN-1)

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OPIOID PRESCRIBING, TITRATION AND MAINTENANCE (1 of 2)

I. GENERAL PRINCIPLES

- The appropriate dose is the dose that relieves the patient's pain throughout its dosing interval without causing unmanageable side effects.
- Calculate increase based upon total opioid dose (Around the clock/scheduled and as needed) taken in the previous 24 h.
- Increase both around the clock and as needed doses. The rapidity of dose escalation should be related to the severity of the symptoms. See Response to Severe or Moderate Pain with Short-Acting Opioids (PAIN-5).

  For example:
  - Pain 7-10 Consider increasing dose by 50%-100%
  - Pain 4-6 Consider increasing dose by 25%-50%
  - Pain 1-3 Consider increasing dose by 25%
- Switch from fixed-combination opioids to single-entity opioids when acetaminophen dose > 4 g/d.
- If patient is experiencing unmanageable side effects and pain is < 4, consider downward dose titration by approximately 25% and reevaluate.
- Equilibrium achieved in about 5 half lifes.

II. APPROXIMATE ORAL AND PARENTERAL DOSE EQUIVALENTS OF OPIOIDS BASED ON SINGLE DOSE DATA

Opioid Analgesic	Oral Dose	Parenteral Dose	Duration of Analgesic Action[4]	Clearance Rate
Codeine[1]	100 mg	50 mg	q 3-4 h	2.9 h
Hydrocodone	15 mg	N/A	q 3-4 h	3.8 ± .3 h
Oxycodone	10 mg	N/A	q 3-4 h	3.2h
Morphine	15 mg	5 mg	q 3-4 h	1.5-2.0 h
Hydromorphone	4 mg	0.75-1.5 mg	q 3-4 h	2.5 h
Levorphanol[1]	2 mg	1 mg	q 6-8 h	11-30 h
Methadone[2]	*	*		
Fentanyl[3]	N/A	50 mcg		1-3 h
Transdermal Fentanyl	N/A	25-50 mcg/h[3]	q 48-72 h	1-3 h

Not Recommended
Propoxyphene
Meperidine[5]
Mixed agonist-antagonist
Partial agonists
Placebos

*Caution is needed with application of this drug and monitoring is required. Due to drug to drug interactions, metabolic issues, potential increased potency, accumulation and cardiac toxicity; consider consultation with a pain management specialist.

[1]Doses above 1.5 mg/kg are not recommended due to increased adverse effects.

[2]Equivalency ratios comparing morphine (and other opioids) to methadone are dose-dependent. This ratio may range from 1:1 at low doses of oral morphine to as high as 20:1 for patients receiving oral morphine in excess of 300 mg per day. Because of its long half-life, high potency, and interindividual variations in pharmacokinetics, methadone should be started at lower doses and titrated upwards carefully with provisioin of adequate breakthrough pain medications during the titration period.

[3]Dosing range: fentanyl, 25-50 mcg/hour q72 h » 90-268 mg oral morphine q 24 h, or q72 h dose of transdermal fentanyl »$^{1}/_{2}$ x mg/day dose of oral morphine.

[4]Recommended dose frequency for immediate release opioids.

[5]Dose equivalency is approximately $^{1}/_{10}$ of morphine.

OPIOID PRESCRIBING AND TITRATION continued on next page

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OPIOID PRESCRIBING, TITRATION and MAINTENANCE (2 of 2)

III. PRINCIPLES OF MAINTENANCE OPIOID THERAPY

- **Consider converting from short-acting opioids to sustained release opioids for control of chronic persistent pain when 24 h opioid requirement is stable:**
  - **Extended-release morphine sulfate tablets every 8-24 h depending on brand. Capsules every 8-24 h**
  - **Extended-release oxycodone hydrochloride tablets every 8-12 h**
  - **Transdermal fentanyl delivery system every 48-72 h**

- **Provide rescue doses of short-acting opioids for pain not relieved by sustained release opioids including acute exacerbations of pain, activity, or position related pain or pain at the end of dosing interval:**
  - **Use short-acting form of sustained release opioid whenever possible**
  - **Allow immediate-release rescue doses of 10% to 20% of 24-h oral dose (mg) every 1 h prn**
  - **The 24 h adult oral morphine dose equivalent of transdermal fentanyl is 2 x mcg/h dose.**
  - **Consider oral transmucosal fentanyl citrate for brief episodes of acute exacerbation of pain not attributed to inadequate dosing of around the clock opioid. Data does not support a specific transmucosal fentanyl dose. Initiate with a 200 mcg unit**

Increase dose of sustained release opioid if patient persistently needs doses of as needed opioids or when dose of around the clock opioid fails to relieve pain at peak effect or at end of dose.

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MANAGEMENT OF OPIOID SIDE EFFECTS (1 of 2)

Constipation

- Preventive measures
  - Prophylactic medications
    - Stimulant laxative + stool softener (senna + docusate, 2 tablets every morning).
    - Increase dose of laxative when increasing dose of opioids
  - Increase fluids
  - Increase dietary fiber
  - Exercise, if appropriate
- If constipation develops
  - Assess for cause and severity of constipation
  - Rule out obstruction
  - Treat other causes
  - Titrate as needed to maximal dose of laxative (senna + docusate, 4 tablets bid) with goal of one non-forced bowel movement every 1-2 d.
  - Consider nonopioid analgesic to allow reduction of the opioid dose (See PAIN-E)
- If constipation persists
  - Reassess for cause and severity of constipation
  - Check for impaction
  - Consider adding another agent, such as magnesium hydroxide, 30-60 mL daily; bisacodyl, 2-3 tablets PO daily, or 1 rectal suppository daily; lactulose, 30-60 mL daily; sorbitol, 30 mL every 2 h x 3, then prn, or magnesium citrate, 8 oz PO daily, polyethelene glycol (1 capful/8 oz water PO bid)
  - Fleet, saline, or tap water enema
  - Consider use of a prokinetic agent (eg, metoclopramide, 10-20 mg PO qid)
  - Consider neuraxial analgesics or neuroablative techniques to potentially reduce opioid dose

Nausea

- Preventive measures
  - Make antiemetics available with opioid prescription
- If nausea develops
  - Assess for other causes of nausea (eg, constipation, central nervous system pathology, chemotherapy, radiation therapy, hypercalcemia)
  - Consider nonopioid analgesic to allow reduction of the opioid dose
  - Consider prochlorperazine, 10 mg PO every 6 h prn; thiethylperazine, 10 mg PO every 6 h prn; haloperidol, 0.5-1.0 mg PO every 6-8 h; or metoclopramide, 10-20 mg PO every 6 h prn
  - If nausea remains on the prn regimen, administer antiemetics around the clock for 1 wk, then change to prn
  - Consider adding a serotonin antagonist (eg, granisetron, 2 mg PO daily, or ondansetron, 8 mg PO tid, or dolasetron 100-200 mg PO, or palonosetron 300 mcg/kg IV)

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MANAGEMENT OF OPIOID SIDE EFFECTS (1 of 2)

Nausea (continued)

- If nausea persists for more than 1 wk
  - Reassess cause and severity of nausea
  - Change opioid
- If nausea persists after a trial of several opioids and above measures
  - Reassess cause and severity of nausea
  - Consider neuraxial analgesics or neuroablative techniques to potentially reduce opioid dose

Sedation

- Preventive measures
  - Initiate opioids at suggested starting doses, appropriate for patient opioid history and clinical status
  - If opioid must be increased, do so by 25%-50%
  - If sedation develops and persists for more than 1 wk after initiating opioids
  - Assess for other causes of sedation (eg, CNS pathology, other sedating medications, hypercalcemia, dehydration, sepsis, hypoxia)
  - Decrease the dose of opioid if pain control can be maintained at a lower dose
  - Consider changing the opioid
  - Consider nonopioid analgesic to allow reduction of the opioid dose
  - Consider a lower dose of opioid given more frequently, to decrease peak concentrations
  - Consider the addition of caffeine, 100-200 mg PO every 6 h; methylphenidate, 5-10 mg 2-4 times per day up to 20 mg per day; or dextroamphetamine, 5-10 mg PO daily
- If sedation persists despite several changes of opioids and the above measures
  - Reassess cause and severity of sedation
  - Consider neuraxial analgesics or neuroablative techniques to potentially reduce opioid dose

Delirium

- Assess for other causes of delirium (eg, hypercalcemia, CNS, metastases, other psychoactive medications, etc.)
- Consider changing the opioid
- Consider nonopioid analgesic to allow reduction of the opioid dose
- Consider haloperidol, 0.5-2 mg PO every 4-6 h or alternative neuroleptic agents

Motor and Cognitive Impairment

- Studies have shown that stable doses (> 2 wk) are not likely to interfere with psychomotor and cognitive function

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SPECIFIC PAIN PROBLEMS

Pain associated with inflammation - Trial of NSAIDs or glucocorticoids

Bone pain without oncologic emergency:

- Trial of opioids and/or NSAIDs
- Local bone pain: consider local radiation therapy or nerve block (eg, rib pain)
- Diffuse bone pain: consider trial of bisphosphonates, hormonal or chemotherapy for responsive tumors, glucocorticoids and/or systemic administration of radioisotopes in selected patients
- Consider physical medicine evaluation See Specialty Consultations (PAIN-I)
- For resistant pain, consider anesthetic procedure (nerve blocks, spinal opioids and anesthetics), orthopedic, or neurosurgical approaches See Specialty Consultations (PAIN-I)

Nerve compression or inflammation - Trial of glucocorticoids

Neuropathic pain:

- Trial of antidepressant: start with low dose and increase every 3-5 days if tolerated or lengthen interval up to 14 days (eg, nortriptyline, 10-150 mg/d; doxepin, 10-150 mg/d; desipramine, 10-150 mg/d; venlafaxine, 37.5-225 mg/d), duloxetine, 20-60 mg/day
  and/or
- Trial of anticonvulsant: start with low dose and increase every 3-5 days if tolerated or lengthen interval up to 14 days (eg, gabapentin, 100-1,200 mg tid; carbamazepine, 100-400 mg bid; pregabalin 50-300 mg bid
  and/or
- Consider topical agents (eg, capsaicin and local anesthetics)
- If results are unsatisfactory after a 2-3 week trial at a reasonable dose, consider referral to a pain service or pain expert, or to an anesthesiologist/neurosurgeon for an appropriate procedure See Interventional Strategies (PAIN-6)

Painful lesions that are likely to respond to antineoplastic therapies:

- Consider trial of radiation, hormones, or chemotherapy
- For severe refractory pain or eminently dying. See NCCN Palliative Care Guideline

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Adult Cancer Pain

PSYCHOSOCIAL SUPPORT

- **Support**
  - Inform patient and family that emotional reactions to pain are normal and are evaluated and treated as part of pain treatment.
  - Provide emotional support to patients and families that acknowledges the pain is a problem to be addressed.
  - Assist in accessing appropriate treatment.
  - State that you will work together with the patient and family as part of the team to address the pain problem.
  - Describe the plan of action to be taken and when results can be expected.
  - Express your commitment to staying available until the pain is better managed.
  - Verbally repeat your concern and the plan of action to be taken.
  - Inform patient and family that there is ALWAYS something else that can be done to try to adequately manage pain and other noxious symptoms.

- **Skills training**
  - Teach coping skills, provide pain relief, enhance a sense of personal control, and refocus psychic energy on optimizing quality of life.
  - Coping skills for pain emergency include Lamaze-type breathing exercises, distraction techniques, and cognitive coping statements to encourage assertiveness and to maximize comfort.
  - Coping skills for chronic pain (not pain emergency) include all of the above plus relaxation techniques, guided imagery, graded task assignments, and hypnosis to maximize function.
  - Educate patient and family that pain management is a team effort. Members of the team include: oncologist, nurse, anesthesiologist, neurologist, psychologist, social worker, psychiatrist, physical therapist and spiritual counselor. See Patient and Family Education (PAIN-G)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Adult Cancer Pain

PATIENT AND FAMILY EDUCATION

- Messages to be conveyed to patient and family
  - Relief of pain is important and there is no benefit to suffering with pain.
  - Pain can usually be well controlled with medications taken by mouth.
  - If these medications do not work, many other options are available.
  - Morphine and morphine-like medications are often used to relieve pain.
    - When these drugs are used to treat cancer pain, addiction is rarely a problem.
    - If you take these medications now, they will still work later.
  - Communication with the doctors and nurses is critical.
    - Doctors and nurses cannot tell how much pain you have unless you tell them.
    - Doctors and nurses want to know about any problems that you think the pain medications may be causing, as there are probably ways to make these better.
    - Please tell your doctor or nurse if you are having any difficulty getting your medication or concerns about taking them. They have dealt with these issues before and will help you.
    - Expect optimal treatment for pain and side effects. Inform patient of right to expect adequate pain treatment.
- The following must be reviewed with each patient and family and provided in written form, which is dated:
  - A list of each medication prescribed, a description of what each medication is for, and instructions as to how and when to take each one
  - A list of potential side effects of these medications and what to do if they occur
  - A list of all medications to be discontinued
  - A list of telephone numbers to reach an appropriate healthcare professional and specific instructions to call regarding:
    - Any problems in getting the prescriptions or taking the medication
    - New pain, change in pain, or pain not relieved with medication
    - Nausea and vomiting that prevents eating for 1 day
    - No bowel movements for 3 days
    - Difficulty arousing the patient from sleep easily during the daytime
    - Confusion
  - A plan for follow-up visits and/or phone calls.

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Adult Cancer Pain

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAID) AND ACETAMINOPHEN PRESCRIBING

Use any NSAID that the patient has found effective and tolerated well in the past.
Otherwise, consider the IV or oral equivalent of ibuprofen at maximum dose.

- **Ibuprofen, 400 mg qid (daily maximum = 3,200 mg),**
- **Compounds that do not inhibit platelet aggregation**
  - **Nonacetylated salicylate**
  - **Choline + magnesium salicylate combinations, 1.5-4.5 g/d in three divided doses**
  - **Salsalate, 2-3 g/d in two or three divided doses**
  - **Selective COX-2 inhibitor**
- **Other nonopioid analgesics**
  - **Acetaminophen, 650 mg every 4 h or 1 gm every 6 h (daily maximum 4 g/d) (use caution with combination products to prevent excess acetaminophen ingestion)**

Use NSAIDS with caution in patients at high risk for GI or renal toxicities.

- **Patients at high risk for**
  - **Renal toxicities: age > 60 y, compromised fluid status, interstitial nephritis, papillary necrosis, and concomitant administration of other nephrotoxic drugs (including cyclosporin, cisplatin) and renally excreted chemotherapy**
  - **GI toxicities: age > 60 y, history of peptic ulcer disease or excess alcohol use, major organ dysfunction, high-dose NSAIDs given for long periods**
- **Monitoring for toxicities**
  - **Baseline blood pressure, BUN, creatinine, CBC, and fecal occult blood**
  - **Repeat every 3 mo to ensure stability**
- **Treatment of toxicities:**
  - **Renal toxicities: discontinue NSAID if BUN or creatinine doubles or if hypertension develops or worsens**
  - **GI toxicities: consider discontinuing NSAID or changing to another agent (eg, selective COX-2 inhibitor, antacids, H_2 receptor antagonists, misoprostol, omeprazole)**

Further NSAID decisions:

- **If two NSAIDs are tried in succession without efficacy, use another approach to analgesia**
- **If NSAIDs are effective but treatment is limited by toxicities that are not deemed serious, consider trial of another NSAID**
- **COX-2 inhibitors are associated with lower incidence of GI side effects and do not inhibit platelet aggregation, however, they have not been demonstrated to have reduced renal side effects.**
- **Toxicity of anti-cancer treatment may increase the risk profile of anti-inflammatory treatment**

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SPECIALTY CONSULTATIONS

Nonpharmacologic consultation

Major indication for referral is:
Pain likely to be relieved or function improved with physical, cognitive or interventional modalities

- **Physical modalities**
  - **Bed, bath, and walking supports**
  - **Positioning instruction**
  - **Physical therapy**
  - **Massage**
  - **Heat and/or ice**
  - **TENS**
  - **Acupuncture or acupressure**
  - **Ultrasonic stimulation**
- **Cognitive modalities**
  - **Imagery/hypnosis**
  - **Distraction training**
  - **Relaxation training**
  - **Active coping training**
  - **Graded task assignments, setting goals, pacing and prioritizing**
  - **Cognitive behavioral training**
  - **Depression/Distress consultation** See NCCN Distress Management Guidelines
  - **Consider pain and palliative care specialty consultation** See NCCN Palliative Care Guidelines
    - **Complex management**
    - **Diagnosis and treatment of underlying condition**
- **Substance abuse and diversion consultation**

See Interventional Strategies (PAIN-6)

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Adult Cancer Pain

SUMMARY OF GUIDELINES UPDATES

The following is a summary of the updates from the 2.2005 version of the Adult Cancer Pain Guidelines:

- **Universal screening for pain (PAIN-1), the panel added a recommendation to include the patient's description of their pain (ie, burning, aching etc).**
- **Changed "Begin educational activities" to "Provide patient and family education" throughout the guideline.**
- **Changed "coanalgesic" to "nonopioid analgesic" throughout the guideline.**
- **Clarified recommendations on (PAIN-5) for patients taking opioids.**
- **Combined Moderate Pain with Severe Pain recommendations (PAIN-5) and deleted the existing page.**
- **Added a recommendation for monitoring of respiratory rate and sedation, consider monitoring oxygen saturation and vital signs. (PAIN-5)**
- **Approximate oral and parental dose equivalents of opioids based on single dose data (PAIN-C)**
  - **Removed the not recommended column from the table and put it in a separate box of its own.**
  - **Changed column title from "Duration of Action" to "Duration of Analgesic Action"**
  - **Changed column title from "Half Life" to "Clearance Rate"**
  - **Compared with American Pain Society dose equivalent chart for consistency**
- **Added trial of duloxetine to the list of antidepressants used for neuropathic pain. (PAIN-E)**
- **Added trail of pregabalin to the list of anticonvulsants used for neuropathic pain. (PAIN-E)**

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Adult Cancer Pain

Manuscript

This manuscript is being updated to correspond with the newly updated algorithm.

NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Pain is one of the most common symptoms associated with cancer. Pain is defined as "an independent and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[1] Cancer pain or cancer-related pain distinguishes pain experienced by cancer patients from that experienced by patients without malignancies. Pain occurs in approximately one quarter of patients with newly diagnosed malignancies, one third of patients undergoing treatment, and three quarters of patients with advanced disease.[2-4] In addition, this is one of the symptoms patients fear most. Unrelieved pain denies them comfort and greatly affects their activities, motivation, interactions with family and friends, and overall quality of life.

The importance of relieving pain and the availability of excellent therapies make it imperative that physicians and nurses caring for these patients be adept at the assessment and treatment of cancer pain.[5-7] This requires familiarity with the pathogenesis of cancer pain; pain assessment techniques; common barriers to the delivery of appropriate analgesia; and pertinent pharmacologic, anesthetic, neurosurgical, and behavioral approaches to the treatment of cancer pain.

The most widely accepted algorithm for the treatment of cancer pain was developed by the World Health Organization (WHO).[8,9] It suggests that patients with pain be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If this is not sufficient, the patient should be escalated to a "weak opioid," such as codeine, and subsequently to a "strong opioid," such as morphine. Although this algorithm has served as an excellent teaching tool, the management of cancer pain is considerably more complex than this three-tiered "cancer pain ladder" suggests.

This clinical practice guideline, developed by the National Comprehensive Cancer Network (NCCN) Adult Cancer Pain panel, is unique in several important ways. First, it contains several required components:

- Pain intensity must be quantified, as the algorithm bases therapeutic decisions on a numerical value assigned to the severity of the pain;
- A formal pain assessment must be performed;
- Reassessment of pain intensity must be performed at specified intervals to ensure that the therapy selected is having the desired effect;
- Psychosocial support must be available; and
- Specific educational material must be provided to the patient.

Second, the guidelines acknowledge the range of complex decisions faced in caring for these patients. As a result, they provide dosing guidelines for NSAIDs, opioids, and ancillary medications. They also provide specific suggestions for the escalation of opioid dosage, management of opioid toxicity, and when and how to proceed to other techniques for the management of cancer pain.

Pathophysiologic Classification

Different types of pain occur in cancer patients. A number of attempts have been made to classify pain according to different criteria. Pain classification includes differentiating between pain associated with tumor, pain associated with treatment, and pain unrelated to either. Acute and chronic pain should also be distinguished from each other when deciding what therapy to use. Therapeutic strategy depends on the pain pathophysiology, which is determined by patient examination and evaluation. There are two predominant mechanisms of pain pathophysiology: nociceptive and neuropathic.[10,11]

Nociceptive pain is the result of injury to somatic and visceral structures and the resulting activation of nociceptors. Nociceptors are present in skin, viscera, muscles, and connective tissues. Pain described as sharp, well localized, throbbing, and pressure-like is somatic nociceptive pain. Pain described as more diffuse, irritating, and cramping is visceral nociceptive pain.

Neuropathic pain results from injury to the peripheral or central nervous system. This type of pain might be described as burning, sharp, or shooting. Examples of neuropathic pain include phantom pain, central pain, and post-therapeutic pain.

Comprehensive Pain Assessment

A comprehensive evaluation is essential to ensure proper pain management. Failure to assess pain is the most common cause of poor pain control. This algorithm begins with the premise that all patients with cancer should be screened (PAIN-1) during the initial evaluation, at regular intervals, and whenever new therapy is initiated.

The standard means for determining how much pain a patient is experiencing relies on a patient's self-report. Severity should be quantified using a 0-10 numerical rating scale, a categorical scale, or the pictorial scale (Wong-Baker Faces Pain Rating Scale) (PAIN-A).[12,13] Faces can be used with patients who have difficulty with the above scales, eg, children, the elderly, and patients with language or cultural differences or other communication barriers.

If the patient has no pain, re-screening should be performed at each subsequent visit. However, if pain is present, a comprehensive pain assessment is initiated (PAIN-1). Continuous re-screenings are the cornerstones for choosing the best therapy.

A comprehensive pain assessment involves a variety of components including a history of the pain; pain intensity; location; pathophysiology (somatic, visceral, or neuropathic); etiology; response to current therapy; the patient's general medical condition; important psychosocial factors; and risk factors for undertreatment of the patient's cancer pain.

Pain history is a very important factor which should be comprehensive and elicited directly from the patient when possible. It requires assessment of pain etiology, intensity, location, thorough history of pain (onset, duration, course, etc.) and its pathophysiology. The psychosocial issues associated with pain should also be determined prior to treatment. The patient's goals and expectations of pain management should be discussed, including level of comfort and function. The evaluation of pain

intensity is a key to pain assessment. To evaluate pain intensity, the patient should be asked how the pain interferes with a lifestyle (at rest; with movement; interference with activities) (PAIN-B).

In addition, a physical examination and review of appropriate laboratory and imaging studies are included in this assessment. This evaluation should enable caregivers to determine if the pain is related to an underlying cause that requires specific therapy. For example, it is inappropriate to provide only opioids to a patient suffering pain from impending epidural cord compression. Without glucocorticoids and local radiation therapy, the pain is unlikely to be well controlled, and the patient will remain at high risk for permanent incontinence and paralysis below the level of the spinal cord compression.

Acute Pain Management

The algorithm distinguishes three levels of pain intensity, based on a 0-10 numerical rating scale (with 10 being the worst pain): severe pain (7-10); moderate pain (4-6); and mild pain (1-3) for acute pain management (PAIN-2).[12] It is important to separate pain related to an oncologic emergency from the pain not related to an oncologic emergency. In addition, the algorithm distinguishes opioid naive patients from patients who have previously or are currently taking opioids for cancer pain.

Opioid naive patients experiencing severe or increased pain should receive rapidly escalating doses of short-acting opioids, a bowel regimen, and Nonopioid analgesics as indicated. Care providers should also provide psychosocial support and begin educational activities. Psychosocial support is needed to ensure that patients encountering common barriers to appropriate pain control (eg, fear of addiction or side effects, inability to purchase opioids) or needing additional assistance (eg, depression, rapidly declining functional status) receive appropriate aid (PAIN-F). An individual approach should be used to determine starting dose, frequency, and titration in order to achieve a balance between analgesia and side effects. Details of prophylactic bowel regimens and antiemetics are provided on page PAIN-D and should begin at the same time with opioid prescription.

Although pain intensity ratings will be obtained frequently to judge opioid dose increases, a formal reassessment is mandated in 24 hours for severe pain. If the pain at this time is unchanged or increased, the working diagnosis must be re-evaluated. In addition, the adequacy of opioid titration must be re-evaluated by calculating and comparing the total parenteral morphine equivalents administered each day.

For patients whose pain is less than 7 at presentation, the pathways are quite similar. The main differences include the option to perform the formal pain intensity reassessment less frequently (24-48 hours) and to consider beginning with slower titration of short-acting opioids for patients with moderate pain intensity rating 4-6 or with an NSAID or acetaminophen if the patient has mild pain intensity rating from 1 to 3 (PAIN-2) and is opioid and NSAID-naive. Reassessment should be performed in 24-72 hours if patient presented with a mild pain (1-3) to determine the subsequent treatment.

The adjuvant analgesics of diverse drug classes are commonly used to help manage bone pain, neuropathic pain, visceral pain and to reduce systemic opioid requirement (PAIN-E). NSAIDs, selective COX-2 inhibitors, tricyclic antidepressants (TCA), anticonvulsant drugs, bisphosphonates, and hormonal therapy are among most commonly used medications. The NSAID and acetaminophen prescribing guidelines are presented on page PAIN-H. History of peptic ulcer disease, advanced age (>60 years old), male gender, and

concurrent corticosteroid therapy should be considered before NSAIDs administration to prevent upper gastrointestinal tract bleeding and perforation. Well-tolerated proton pump inhibitors are recommended to prevent gastrointestinal side-effects induced by NSAIDs. NSAIDs should be prescribed with caution in patients older than 60 years of age or in those having compromised fluid status, interstitial nephritis, concomitant administration of other nephrotoxic drugs, and renally excreted chemotherapy in order to prevent renal toxicities.

Selecting an Appropriate Opioid and Route of Administration

Before starting therapy, determine the underlying pain mechanism and diagnose the pain syndrome. Appropriate opioid selection may be difficult and depends on patients' pain intensity and any current analgesic therapy. Morphine, hydromorphone, fentanyl, oxycodone are the opioids commonly used in the United States. A balance between analgesia and side effects might be achieved by changing to an equivalent dose of an alternative opioid. This approach, known as opioid rotation, is now a widely accepted technique used to address poorly responsive pain.[14] Relative effectiveness is important to consider when switching between oral and parenteral routes to avoid subsequent overdosing or underdosing. Equianalgesic dose ratios, opioid titration and maintenance are shown in the algorithm (PAIN-C). For example, the morphine/hydromorphone ratio is about 5 for parenteral dose administration (5 mg of morphine equal to 0.75-1.5 mg of hydromorphone), which should be considered during opioid rotation.

Individual variations in methadone pharmokinetics (long half-life ranging from 8 to more than 120 hours) make its usage very difficult in cancer patients. Because of its long half-life, high potency, and interindividual variations in pharmacokinetics, methadone should be started at lower doses and titrated upwards slowly with provision of adequate breakthrough pain medications during the titration period. Consultation with a pain management specialist should be considered before its application.

Propoxyphene, meperidine, mixed agonist-antagonists, partial agonists, and placebos are not recommended for cancer patients. Meperidine and propoxyphene are not recommended in patients with impaired renal function or dehydration, because they may also cause neurotoxicity.[15] Pure agonists (such as codeine, oxycodone, oxymorphone and fentanyl) are the most commonly used medications in the management of cancer pain. The short half-life opioid agonists (morphine, hydromorphone, fentanyl, and oxycodone) are preferred, because they have the ability to titrate more easily than the long half-life analgesics.[16]

The following methods of continuous infusion are widely used in clinical practice: “around the clock”, “as needed”, and “patient-controlled analgesia”. “Around the clock” dosing is provided to chronic pain patients for continuous pain relief. A “rescue dose” should be provided as a subsequent treatment for patients receiving these controlled-release medications. Rescue doses of short-acting opioids should be provided for pain that is not relieved by sustained/controlled release opioids (PAIN-C, 2 of 2). Opioids administered on an “as needed” basis are for patients who have intermittent pain with pain-free intervals. The “as needed” method is also used when rapid dose escalation is required. The patient-controlled analgesia (PCA) technique allows a patient to control a device that delivers a bolus of analgesic “on demand” (according to and limited by parameters set by a physician).

The least invasive, easiest, and safest route of opioid administration should be provided to ensure adequate analgesia. Oral is the preferred route of administration for chronic opioid therapy.[16-18] The

oral route should be considered first in patients who can take oral medications unless a rapid onset of analgesia is required or the patient experiences side-effects associated with the oral administration. Continuous parenteral infusion (IV or SC) is recommended for patients who cannot swallow or absorb opioids.

For patients with a pain rating between 7-10 or patients in a pain crisis, the initial oral dose of 5-15 mg of morphine sulfate or equivalent is recommended for patients not already taking opiods. For patients currently on opioid therapy, the previous 24-hour dose and breakthrough dose (10%-20% of 24-hour dose) should be calculated. The breakthrough dose should be increased by 50%-100% and administered. Reassessment should be performed every 60 minutes to determine subsequent dose (PAIN-5).

Intravenous loading dose for patients with severe (7-10) and moderate (4-6) pain or for pain crisis depends on prior administration of opioids. The dose 1-5 mg of intravenous morphine sulfate or equivalent is recommended for opioid-naive patients with severe pain or for pain crisis (PAIN-5). For patients currently taking opioids a dose increase of 10-20% of daily intravenous morphine equivalent is recommended. Reassessment should be performed every 15 minutes to calculate the subsequent dose of opioids. The subsequent dose of opioids for intravenous administration depends on the pain score after 15-minute reassessment.

For patients with a pain rating between 4-6 who are not taking opioids, the initial oral dose of 5-15 mg of morphine sulfate or equivalent is recommended. A dose increase of 25-50% of daily oral morphine equivalent is recommended as the initial dose for patients who experience moderate pain at presentation and who are currently taking opioids. Reassessment for this category of patients should be performed every 4 hours. A dose increase of 25%-50% of daily oral morphine equivalent should be considered for patients not taking opioids with pain score decrease less than 50% after a 4-hour reassessment of the initial treatment. If the pains score decreases 50% or more after a 4-hour reassessment of the initial treatment, then the initial dose is considered "effective" and should be administered every 4 hours (PAIN-6).

After the initial response and treatment of acute pain, the patient should have a comprehensive reassessment. If an acceptable level of comfort and function has not been achieved for the patient, the NCCN Adult Cancer Pain panel recommends possible conversion to sustained-release medication with breakthrough dosing, Nonopioid analgesics, management of side-effects, interventional procedures, and psychosocial and educational interventions (PAIN-3). The subsequent treatment is based upon the patient's continued pain rating score.

Subsequent follow-up is recommended if the patient goals/expectations are achieved or for patients with mild (1-3) pain after comprehensive reassessment of the initial pharmacologic management (PAIN-4). Frequency for the routine follow-up should be set for at least every 3 months depending on patient conditions and institutional standards. Patients should be provided with a written follow-up plan and instructed on the importance of the adherence to medication plan, maintain clinic appointments, and follow-up with clinicians (PAIN-4).

Interventional Strategies

Some patients experience inadequate pain control despite pharmacological therapy or may not tolerate an opioid titration program because of side effects. Some patients may prefer procedural options instead of a chronic medication regimen. Several

interventional strategies are available if a patient does not achieve adequate analgesia. Regional infusion of analgesics (epidural, intrathecal, and regional plexus), neuroablative procedures for well-localized pain syndromes (eg, facet or sacro-iliac joint pain or visceral pain, use celiac/superior hypogastric plexus neurolysis), percutaneous vertebro/kyphoplasty, percutaneous disk decompression, and neurostimulation procedures (ie, peripheral neuropathy) have proven successful in pain management (PAIN-7). These techniques have been demonstrated, in some cases, to eliminate the pain complaint or significantly reduce the level of pain to allow a significant decrease in analgesic medication requirements. The intrathecal route of opioid administration should be considered in patients with intolerable somnolence and/or confusion. This approach is a valuable tool to improve analgesia for patients who have pain from a variety of anatomical locations (eg, head and neck, upper and lower extremities, trunk).[19]

Additional Therapies

Additional strategies specific to the pain situations can be considered. Specific recommendations for inflammatory pain, bone pain, nerve compression or inflammation, neuropathic pain, and pain that is likely to respond to antineoplastic therapies are provided (PAIN-E). Overall, neuropathic pain is less responsive to opioids than pain caused by other pathophysiologies.

Other therapies, including specific non-traditional analgesic drugs, are usually indicated for neuropathic pain syndrome.[20] For example, a patient with neuropathic pain who failed to gain sufficient relief from opioids would be given a trial of an anticonvulsant or tricyclic antidepressant, whereas a patient with pancreatic cancer who was not tolerating opioids or not receiving adequate analgesia would be offered a celiac plexus block.

Nonpharmacologic specialty consultations for physical modalities (eg, massage, physical therapy) and cognitive modalities (eg, hypnosis, relaxation) may provide extremely beneficial adjuncts to pharmacologic interventions (PAIN-I).

Attention should also be focused on psychosocial support (PAIN-F), educational activities (PAIN-G), and reducing the side effects of the analgesics. Side effects such as constipation; nausea; sedation; opioid-induced neurotoxicity (delirium, agitation, myoclonus, and hyperalgesia); and motor and cognitive impairment in cancer patients are very common due to drug combinations. Proper management is necessary to prevent and reduce these side effects (PAIN-D). In addition, continued pain ratings should be obtained and documented in the medical record to ensure that the patient's pain remains under good control and goals of treatment are achieved. In addition, specialty consultations can be helpful in providing interventions to assist with difficult cancer pain problems.

Summary

In most patients, cancer pain can be successfully controlled with appropriate techniques and safe drugs. The overall approach to pain management encompassed in these guidelines is comprehensive. It is based on objective pain assessments, utilizes both pharmacologic and nonpharmacologic interventions, and requires continual reevaluation of the patient. The NCCN Adult Cancer Pain panel believes that cancer pain can be well controlled in the vast majority of patients if the algorithms presented are systematically applied, carefully monitored, and tailored to the needs of the individual patient.

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